Radiotherapy and Oncology 177 (2022) 134–142

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Trends and variation in the use of radiotherapy in non-metastatic prostate cancer: A 12-year nationwide overview from the Netherlands

Jelle Evers [a,b,*], Linda G.W. Kerkmeijer [c,1], Roderick C.N. van den Bergh [d], Maurice J.C. van der Sangen [e], Maarten C.C.M. Hulshof [f,1], Monique C.W.M. Bloemers [g,2], Sabine Siesling [a,b], Mieke J. Aarts [a], Katja K.H. Aben [a,h], Henk Struikmans [i]

[a] Netherlands Comprehensive Cancer Organisation (IKNL), Department of Research and Development, Godebaldkwartier 419, 3511 DT Utrecht; [b] University of Twente, Department of Health Technology and Services Research, Technical Medical Center, Hallenweg 5, 7522 NH Enschede; [c] Radboud University Medical Center, Department of Radiation Oncology, Geert Grooteplein Zuid 10, 6525 GA Nijmegen; [d] St. Antonius Hospital, Department of Urology, Koekoekslaan 1, 3435 CM Nieuwegein; [e] Catharina Hospital, Department of Radiation Oncology, Michelangelolaan 2, 5623 EJ Eindhoven; [h] Radboud University Medical Center, Radboud Institute for Health Sciences, Geert Grooteplein Zuid 21, 6525 EZ Nijmegen; and [i] Leiden University Medical Center, Department of Radiation Oncology, Albinusdreef 2, 2333 ZA Leiden, the Netherlands

ARTICLE INFO

Article history:
Received 8 July 2022
Received in revised form 28 September 2022
Accepted 22 October 2022
Available online 31 October 2022

Keywords:
Prostatic neoplasms
Radiotherapy
Brachytherapy
Prostatectomy
Watchful waiting
Epidemiology

ABSTRACT

Purpose: This population-based study describes nationwide trends and variation in the use of primary radiotherapy for non-metastatic prostate cancer in The Netherlands in 2008–2019.
Methods: Prostate cancer patients were selected from the Netherlands Cancer Registry (N = 103,059). Treatment trends were studied over time by prognostic risk groups. Multilevel analyses were applied to identify variables associated with external beam radiotherapy (EBRT) and brachy-monotherapy versus no active treatment in low-risk disease, and EBRT versus radical prostatectomy in intermediate and high-risk disease.
Results: EBRT use remained stable (5–6%) in low-risk prostate cancer and increased from 21% to 32% in intermediate-risk, 37% to 45% in high-risk localized and 50% to 57% in high-risk locally advanced disease. Brachy-monotherapy decreased from 19% to 6% and from 15% to 10% in low and intermediate-risk disease, respectively, coinciding an increase of no active treatment from 55% to 73% in low-risk disease. Use of EBRT or brachy-monotherapy versus no active treatment in low-risk disease differed by region, T-stage and patient characteristics. Hospital characteristics were not associated with treatment in low-risk disease, except for availability of brachy-monotherapy in 2008–2013. Age, number of comorbidities, travel time for EBRT, prognostic risk group, and hospital characteristics were associated with EBRT versus prostatectomy in intermediate and high-risk disease.
Conclusion: Intermediate/high-risk PCa was increasingly managed with EBRT, while brachy-monotherapy in low/intermediate-risk PCa decreased. In low-risk PCa, the no active treatment-approach increased. Variation in treatment suggests treatment decision related to patient/disease characteristics. In intermediate/high-risk disease, variation seems furthermore related to the treatment modalities available in the diagnosing hospitals.

Prostate cancer (PCa) is one of the most frequently diagnosed types of cancer among men in Western countries [1]. In recent years, approximately 12,500 men in The Netherlands were diagnosed with PCa annually, ~75 % of whom with non-metastatic disease [2]. Non-metastatic PCa includes both localized and locally advanced disease and is classified in prognostic risk groups, which in The Netherlands are generally based on the European Association of Urology (EAU) classification [3].

Radiotherapy is a treatment option in all risk groups. In low-risk PCa, however, deferred treatment with active surveillance has been preferred since ~ 2009/2010 in selected patients and thereafter in all patients with low-risk PCa [3–5], as the harm of immediate treatment outweighs the benefits [6]. Also in intermediate-risk PCa active surveillance can be considered, but only for patients with favorable tumor characteristics [3–5]. In most patients with

Abbreviations: NCR, Netherlands Cancer Registry.

* Corresponding author at: Godebaldkwartier 419, 3511 DT Utrecht, the Netherlands.
E-mail address: J.Evers@iknl.nl (J. Evers).

[1] On behalf of the Dutch Association of Radiation Oncology (NVRO), division of Urological Cancers (LPRU).

[2] On behalf of the Dutch Association of Radiation Oncology (NVRO), general board.

https://doi.org/10.1016/j.radonc.2022.10.028
0167-8140/

intermediate-risk PCa, external beam radiotherapy (EBRT) – with or without hormonal androgen deprivation therapy (ADT) and/or brachytherapy-boost – is a recommended curative-intent treatment strategy, as are brachy-monotherapy and radical prostatectomy (RP) [3–5]. In high-risk PCa, EBRT combined with long term ADT and optionally a brachytherapy-boost, as well as RP followed by salvage EBRT in case of residual disease, are recommended [3–5]. Since high-quality evidence concluding superiority of either radiotherapy or RP is lacking, patients' preferences and tumor characteristics should drive the choice in treatment in intermediate and high-risk disease [7,8]. Watchful waiting can be considered in any risk group when life expectancy is limited or definitive treatment is not feasible [3–5].

Within Western countries considerable variation in radiotherapy use in non-metastatic PCa has been observed [9–13]. This suggests that the choice of treatment is based on local protocols, physician and/or patient preferences, and the availability of treatment modalities. In recent decades, the availability of radiotherapy and RP has changed in The Netherlands. Since 2008, thirteen additional EBRT facilities have opened, resulting in eighteen institutes performing EBRT in thirty-three facilities, and the number of facilities performing brachytherapy declined. Also hypofractionated EBRT was implemented for low and intermediate-risk PCa. Moreover, robot-assisted RP became widely available and a minimum volume norm for RP has been introduced (>20 annually since 2012, >50 since 2018 and $\geq$ 100 since 2019). These developments and the implemented recommendation of active surveillance in low-risk disease, may have changed the previously reported use of radiotherapy for PCa in The Netherlands [9,14–16].

No nationwide overview of trends and variation in the use of radiotherapy as part of non-metastatic PCa treatment is available for the period since 2008. This nationwide study aims to investigate trends and variation in the use of radiotherapy versus other treatment approaches in low-risk, intermediate-risk, and high-risk localized PCa as well as locally advanced PCa in 2008–2019 in The Netherlands.

Materials and methods

Patients

Patients diagnosed with localized (cT1-2 cN0) or locally advanced (cT3-4 cN0/cT1-4 cN1) PCa in 2008–2019, who could be assigned an EAU prognostic risk group (see Definitions section), were selected from the Netherlands Cancer Registry (NCR). The population-based NCR contains information on patients, disease, and primary treatment of all patients diagnosed with cancer in The Netherlands. These data were extracted from Dutch hospitals' medical records by trained registrars. Pathologically and clinically diagnosed patients were included. Patients living, diagnosed, or treated abroad, or diagnosed during autopsy or cystoprostatectomy were excluded.

Definitions

Clinical T-stage (cT) was based on TNM6 (2008–2009), TNM7 (2010–2016) and TNM8 (2017–2019). Prostate specific antigen values (PSA) at time of diagnosis were available. Gleason scores (GS) were based on biopsy specimens, except for patients diagnosed before 2013 who underwent an RP. For them GS were based on the RP specimen.

Table 1
Characteristics of patients diagnosed with prostate cancer in 2008–2019 in The Netherlands, stratified for low, intermediate and high-risk localized and locally advanced prostate cancer.

	Localized						Locally advanced	
	Low-risk		Intermediate-risk		High-risk			
	N = 22,784		N = 37,767		N = 17,777		N = 24,731	
	n	(%)	n	(%)	n	(%)	n	(%)
Year of diagnosis								
2008–2010	5,208	(22.9)	8,852	(23.4)	4,890	(27.5)	5,081	(20.5)
2011–2013	6,016	(26.4)	10,038	(26.6)	4,663	(26.2)	6,174	(25.0)
2014–2016	5,733	(25.2)	8,452	(22.4)	3,796	(21.4)	6,670	(27.0)
2017–2019	5,827	(25.6)	10,425	(27.6)	4,428	(24.9)	6,806	(27.5)
Age at time of diagnosis, years								
< 65	9,409	(41.3)	11,344	(30.0)	3,469	(19.5)	5,260	(21.3)
65– < 75	11,053	(48.5)	18,988	(50.3)	7,561	(42.5)	11,262	(45.5)
$\geq$ 75	2,322	(10.2)	7,435	(19.7)	6,747	(38.0)	8,209	(33.2)
Median age at diagnosis (p25, p75)	66.0	(61.0–71.0)	68.0	(63.0–73.0)	72.0	(66.0–78.0)	71.0	(66.0–76.0)
Geographical region								
North	2,937	(12.9)	5,030	(13.3)	2,550	(14.3)	2,670	(10.8)
East	3,374	(14.8)	5,980	(15.8)	2,719	(15.3)	4,765	(19.3)
South	5,755	(25.3)	8,765	(23.2)	3,864	(21.7)	5,637	(22.8)
South West	5,245	(23.0)	8,296	(22.0)	4,207	(23.7)	5,197	(21.0)
North West	5,473	(24.0)	9,696	(25.7)	4,437	(25.0)	6,462	(26.1)
Hospital of diagnosis								
University hospital [A]	1,362	(6.0)	2,801	(7.4)	1,108	(6.2)	1,749	(7.1)
Radiotherapy department embedded	3,993	(17.5)	7,194	(19.1)	3,109	(17.5)	5,000	(20.2)
Performed brachytherapy	2,657	(11.7)	4,782	(12.7)	1,930	(10.9)	3,361	(13.6)
Performed prostatectomies	14,463	(63.5)	23,740	(62.9)	11,111	(62.5)	15,322	(62.0)
Comorbidities at diagnosis being assessed [B]	3,908	(17.2)	5,734	(15.2)	2,749	(15.5)	4,042	(16.3)
At least 1 comorbidity present	2,318	(59.3)	3,701	(64.5)	1,996	(72.6)	2,891	(71.5)
Median number of comorbidities (p25,p75)	1.0	(0.0–1.0)	1.0	(0.0–2.0)	1.0	(0.0–2.0)	1.0	(0.0–2.0)
Most frequent comorbidities								
Hypertension	1,209	(30.9)	1,938	(33.8)	983	(35.8)	1,440	(35.6)
Diabetes Mellitus	388	(9.9)	694	(12.1)	453	(16.5)	621	(15.4)
Myocardial Infarction	344	(8.8)	581	(10.1)	375	(13.6)	570	(14.1)

p25: 25th percentile, p75: 75th percentile.
[A] Including the single cancer specific hospital in The Netherlands.
[B] Comorbidities were available for patients diagnosed in the South before 2015 and for all patients diagnosed in Q4 2015-Q1 2016.

The EAU classification for prognostic risk groups was applied [3]. However, to reflect the risk stratification frequently applied in Dutch clinical practice, we considered cT2c-tumors with only low or intermediate-risk features as intermediate-risk. Low-risk disease was consequently defined as cT1-2a-tumors with GS < 7 and PSA < 10 ng/ml; intermediate-risk disease as cT2b-c-tumors or GS 7 or PSA 10-20 ng/ml; and high-risk disease as GS > 7 or PSA > 20 ng/ml or locally advanced disease (cT3-4 cN0/cT1-4 cN1).

EBRT was defined as EBRT +/- hormonal therapy +/- brachytherapy-boost. Brachy-monotherapy was defined as brachytherapy +/- hormonal therapy but without EBRT or RP. RP was defined as prostatectomy +/- radiotherapy +/- hormonal therapy. No active treatment included both active surveillance and watchful waiting.

To assess variation across the country, we divided The Netherlands into five geographical regions based on patients' residence, each including $\geq$ 11 hospitals of which $\geq$ 1 university hospital and $\geq$ 3 radiotherapy institutes. We calculated patients' travel time for a one-way car trip to the nearest EBRT facility, using the postal codes of radiotherapy facilities and patient residency and the 2013-GEODAN drive time matrix [17].

For each patient, we classified whether the diagnosing hospital at time of diagnosis 1) was a university medical center, 2) had a radiotherapy department in its organization (not including other institute's departments in the same building), 3) had brachytherapy facilities available in its radiotherapy department, and 4) performed RPs. Also, the hospital's number of low-risk and intermediate/high-risk PCa diagnoses in 2008–2013 and 2014–2019 were determined and used to categorize half of the hospitals as low and half as high-volume.

Comorbidities at the time of diagnoses were registered for patients diagnosed before 2015 in the South of The Netherlands (~15 %) and at national level for patients diagnosed in October 2015-March 2016 [16].

Analyses

Patient and disease characteristics, as well as trends and frequencies of primary treatment over time and by five-year age groups, were described stratified for low, intermediate, and high-risk localized and locally advanced disease. Distribution of treatment by age groups were further stratified for 2008–2013 and 2014–2019, allowing for comparison of treatment distributions in the older and most recent years. Only results for age groups with $\geq$ 50 patients were presented.

Variations in treatment were assessed by identifying associations of patient, tumor, and hospital-related variables with treatment in multilevel adjusted analyses. In low-risk PCa, associations with 1) EBRT versus no active treatment and 2) brachy-monotherapy versus no active treatment were assessed. In intermediate and high-risk PCa, associations with EBRT versus RP were assessed. As treatment options were largely similar, intermediate and high-risk PCa, including locally advanced disease, were combined in these analyses.

Distinct models were created for each association investigated, stratified for 2008–2013 and 2014–2019 to allow for comparing

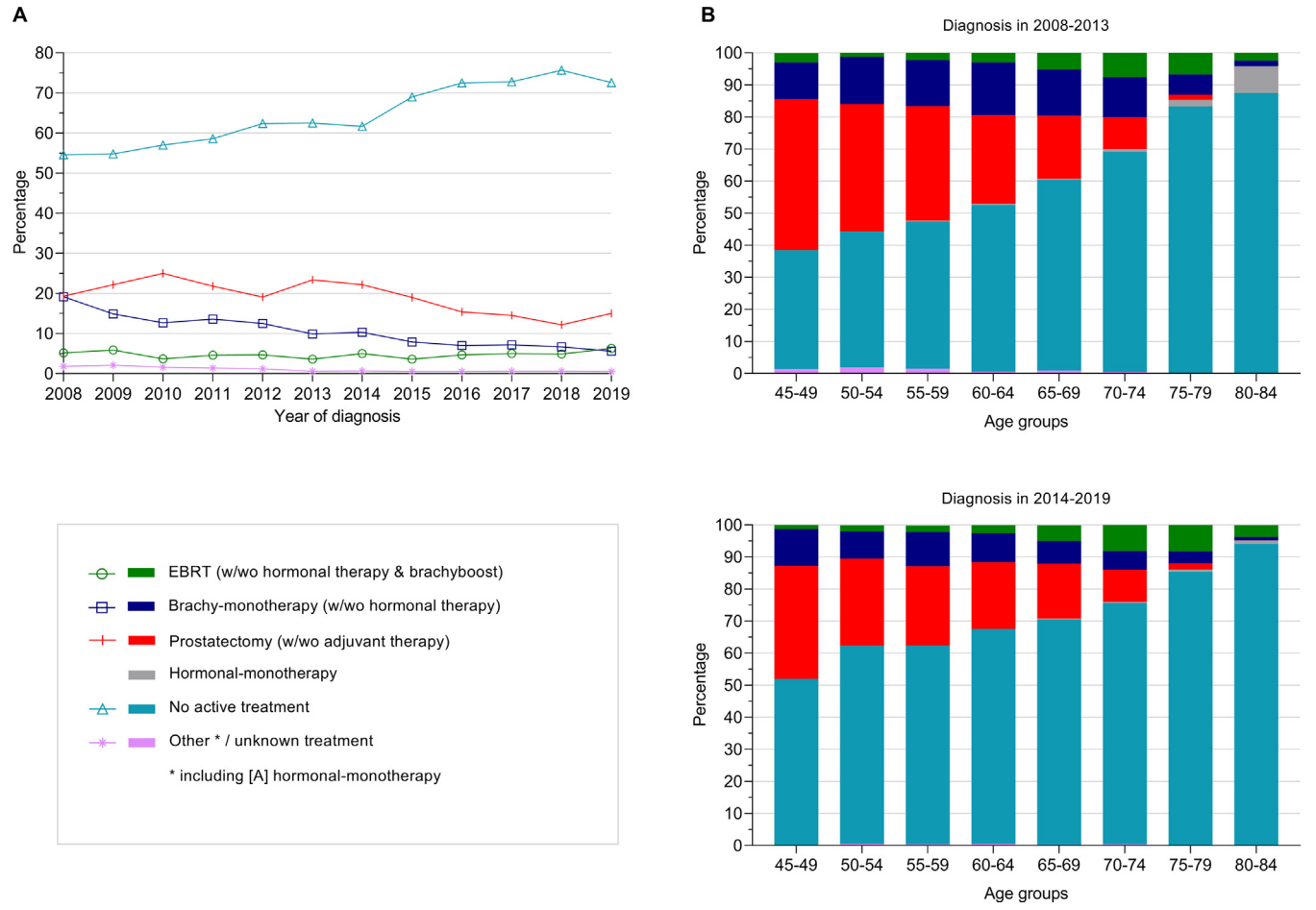

Fig. 1. Primary treatment in patients diagnosed with low-risk localized prostate cancer in The Netherlands [A] over the years of diagnosis, N = 22,784, and [B] according to 5-year age groups stratified for 2008–2013, N = 11,154, and 2014–2019, N = 11,525.

Table 2
Adjusted odds ratios (OR) of receiving EBRT versus no active treatment and brachytherapy versus no active treatment in patients with low-risk localized prostate cancer in The Netherlands, stratified for diagnoses in 2008–2013 and 2014–2019.

OR for receiving EBRT versus no active treatment				
	2008–2013 EBRT N = 516, No active treatment N = 6570		2014–2019 EBRT N = 568, No active treatment N = 8196	
	OR [A]	(95 %CI)	OR [A]	(95 %CI)
Year of diagnosis (continuously)	**0.90**	**(0.85–0.95)**	1.05	(1.00–1.11)
Age at time of diagnosis, years				
< 65	Reference		Reference	
65– < 75	**1.67**	**(1.35–2.07)**	**2.29**	**(1.82–2.87)**
≥ 75	1.06	(0.77–1.46)	**2.14**	**(1.59–2.87)**
Number of comorbidities at diagnosis [B]				
0	Reference		Reference	
1	**1.87**	**(1.06–3.30)**	**4.34**	**(2.06–9.15)**
≥2	1.66	(0.89–3.10)	**5.37**	**(2.55–11.28)**
Geographical region				
North	Reference		Reference	
East	**0.49**	**(0.30–0.80)**	**0.47**	**(0.30–0.74)**
South	**0.55**	**(0.35–0.86)**	**0.51**	**(0.33–0.79)**
South West	0.70	(0.45–1.08)	**0.62**	**(0.41–0.94)**
North West	**0.48**	**(0.31–0.74)**	**0.48**	**(0.32–0.71)**
Travel time (car) for EBRT, minutes				
< 15	Reference		Reference	
15–30	1.09	(0.82–1.44)	1.21	(0.98–1.49)
> 30	1.41	(0.96–2.06)	1.09	(0.74–1.60)
Clinical T-stage				
T1	Reference		Reference	
T2a	**2.54**	**(2.01–3.23)**	**2.14**	**(1.73–2.65)**
Type of hospital				
University [C]	Reference		Reference	
Non-university	1.31	(0.76–2.28)	1.38	(0.78–2.42)
Radiotherapy department in the hospital				
No	Reference		Reference	
Yes	0.70	(0.47–1.05)	1.11	(0.68–1.82)
Volume of low-risk PCa diagnoses in the hospital [D]				
Low volume	Reference		Reference	
High volume	0.89	(0.65–1.21)	1.11	(0.80–1.55)
OR for receiving brachytherapy versus no active treatment				
	2008–2013 Brachytherapy N = 1531, No active treatment N = 6570		2014–2019 Brachytherapy N = 852, No active treatment N = 8196	
	OR [E]	(95 %CI)	OR [E]	(95 %CI)
Year of diagnosis (continuously)	**0.88**	**(0.85–0.91)**	**0.87**	**(0.83–0.91)**
Age at time of diagnosis, years				
< 65	Reference		Reference	
65– < 75	**0.63**	**(0.56–0.71)**	**0.60**	**(0.50–0.72)**
≥ 75	**0.16**	**(0.12–0.22)**	**0.26**	**(0.18–0.37)**
Number of comorbidities at diagnosis [B]				
0	Reference		Reference	
1	0.82	(0.60–1.13)	0.83	(0.55–1.26)
≥ 2	0.80	(0.56–1.15)	1.01	(0.66–1.55)
Geographical region				
North	Reference		Reference	
East	1.30	(0.78–2.17)	1.53	(0.93–2.53)
South	1.09	(0.64–1.89)	**1.86**	**(1.12–3.09)**
South West	1.00	(0.58–1.70)	1.46	(0.88–2.41)
North West	0.90	(0.54–1.49)	1.17	(0.71–1.91)
Clinical T-stage				
T1	Reference		Reference	
T2a	**2.04**	**(1.69–2.45)**	**2.12**	**(1.75–2.57)**
Type of hospital				
University [C]	Reference		Reference	
Non-university	1.45	(0.71–2.94)	1.22	(0.62–2.41)
Brachytherapy is performed in the hospital				
No	Reference		Reference	

(*continued on next page*)

Table 2 (*continued*)

OR for receiving EBRT versus no active treatment				
	2008–2013 EBRT N = 516, No active treatment N = 6570		2014–2019 EBRT N = 568, No active treatment N = 8196	
	OR [A]	(95 %CI)	OR [A]	(95 %CI)
Yes	**1.75**	**(1.03–2.98)**	1.35	(0.03–52.75)
Volume of low-risk PCa diagnoses in the hospital [D]				
Low volume	Reference		Reference	
High volume	1.27	(0.87–1.84)	1.11	(0.78–1.57)

OR: odds ratio, EBRT: external beam radiotherapy, 95 %CI: 95 % confidence interval, PCa: prostate cancer; values in bold are statistically significant.

[A] Models with both a random intercept and random effect were applied for the analyses on travel time for EBRT (2008–2013) and clinical T-stage. The analyses on year of diagnosis, travel time for EBRT (2014–2019), clinical T-stage, and volume of diagnoses in the hospital were not adjusted, as none of the variables fulfilled the criteria for inclusion in the adjustment set. The analysis on number of comorbidities (2008–2013) was adjusted for clinical T-stage and age. The analysis on number of comorbidities (2014–2019) was adjusted for age. The analyses on age, region, travel time for EBRT (2008–2013), type of hospital (2014–2019), and radiotherapy department in the hospital (2008–2013) were adjusted for clinical T-stage. The analysis on type of hospital (2014–2019) was adjusted for clinical T-stage and region. The analysis on radiotherapy department in the hospital (2014–2019) was adjusted for type of hospital and travel time for EBRT. Comorbidities were not included in adjustment sets considering their limited availability. The analysis on type of hospital was not adjusted for a radiotherapy department in the hospital, as this was considered a basic component of university hospitals.

[B] Comorbidities were available for patients diagnosed in the South before 2015 and for all patients diagnosed in October 2015-March 2016.

[C] Including the single cancer specific hospital in The Netherlands.

[D] Patients diagnosed in the 50 % of hospitals with the lowest annual average number of low-risk prostate cancer diagnoses: < 21 patients, were categorized in low volume. The remaining patients in the high volume-category.

[E] Models with both a random intercept and random effect were applied for the analyses on age (2014–2019), clinical T-stage and brachytherapy performed in the hospital (2014–2019). The analyses on year of diagnosis, and volume of diagnoses in the hospital were not adjusted, as none of the variables fulfilled the criteria for inclusion in the adjustment set. The analyses on number of comorbidities, and clinical T-stage were adjusted for age. The analyses on age (2008–2013), and region (2014–2019) were adjusted for clinical T-stage. The analysis on age (2014–2019) was adjusted for year of diagnosis and clinical T-stage. The analysis on region (2008–2013) was adjusted for age and brachytherapy performed in the hospital. The analysis on type of hospital (2008–2013) was adjusted for year of diagnosis, age, brachytherapy performed in the hospital and volume of diagnoses in the hospital. The analysis on type of hospital (2014–2019) was adjusted for clinical T-stage, age, brachytherapy performed in the hospital and volume of diagnoses in the hospital. The analysis on brachytherapy performed in the hospital was adjusted for type of hospital. Comorbidities were not included in adjustment sets considering their limited availability.

the older and most recent years. A model included a random effect and random intercept for the various hospitals if the AICc-fit statistic improved, compared to the model with only a random intercept. This multilevel approach corrected for nesting of patients in hospitals. In addition, sets of variables for adjustment were selected for each investigated association separately (see footnotes of the applicable Tables). Variables were included when univariable inclusion resulted in at least 5 % change in the odds ratio (OR) of interest compared to the unadjusted multilevel OR. Ninety-five percent confidence intervals (95 %CI) were calculated and reflect probable OR-estimates, using a p-value (two-sided) of 0.05 as critical level for statistically significance. Analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

A total of 131,910 men were diagnosed with PCa in 2008–2019. This study includes 103,059 men with non-metastatic PCa; 22 %, 37 %, and 17 % with low, intermediate, and high-risk localized PCa, respectively, and 24 % with locally advanced PCa. Patients with low-risk PCa were younger (median: 66 years) compared to those with intermediate-risk (68 years), high-risk localized (72 years) and locally advanced disease (71 years). Distribution of region and hospital characteristics were largely similar across the risk groups (Table 1).

In low-risk disease, EBRT remained stable over time (5–6 %) and was most frequently applied in men aged 70–79 years (Fig. 1). Brachy-monotherapy and RP decreased from 19 % (2008) to 6 % (2019) and from 19 % to 15 %, respectively, while management with no active treatment increased from 55 % to 73 %. With increasing age, more patients received no active treatment whereas less received brachy-monotherapy or RP.

In multilevel analyses in low-risk PCa, higher cT, higher age and more comorbidities were positively associated with EBRT versus no active treatment in both 2008–2013 and 2014–2019 (Table 2). Living in the North of The Netherlands was associated with a higher probability of EBRT. Only in 2008–2013, year of diagnosis was associated with EBRT versus no active treatment; over time patients were less likely to receive EBRT. For all other variables no clear associations with EBRT were found.

Brachy-monotherapy use in low-risk PCa decreased by year in multilevel analyses (Table 2). Lower age and higher cT were positively associated with brachytherapy versus no active treatment in both 2008–2013 and 2014–2019. Patients in the South compared to the North were more likely to receive brachytherapy in 2014–2019. Only in the period 2008–2013, being diagnosed in a hospital that performed brachytherapy was associated with a higher probability of receiving brachytherapy instead of no active treatment. No clear associations with brachytherapy were found for other variables.

In intermediate-risk disease, EBRT increased from 21 % (2008) to 32 % (2019) (Fig. 2). This increase occurred mainly in men aged 75–84 years. Brachy-monotherapy use decreased from 15 % to 10 %, while the application of RP varied between 33–41 %. A quarter of patients – mainly elderly – received no active treatment; this proportion remained stable over time.

In high-risk localized disease, EBRT and RP increased from 37 % (2008) to 45 % (2019) and 24 % to 34 %, respectively (Fig. 3.1). Adjuvant EBRT was applied in 6 % of RPs. EBRT use mainly increased in men aged 75–84 years, while younger men more frequently underwent RP. Hormonal-monotherapy decreased from 21 % to 7 %. One sixth of patients received no active treatment, which remained stable over time. Most patients receiving hormonal-monotherapy or no active treatment were elderly.

In locally advanced disease, EBRT and RP increased from 50 % (2008) to 57 % (2019) and 7 % to 15 %, respectively (Fig. 3.2). Seven

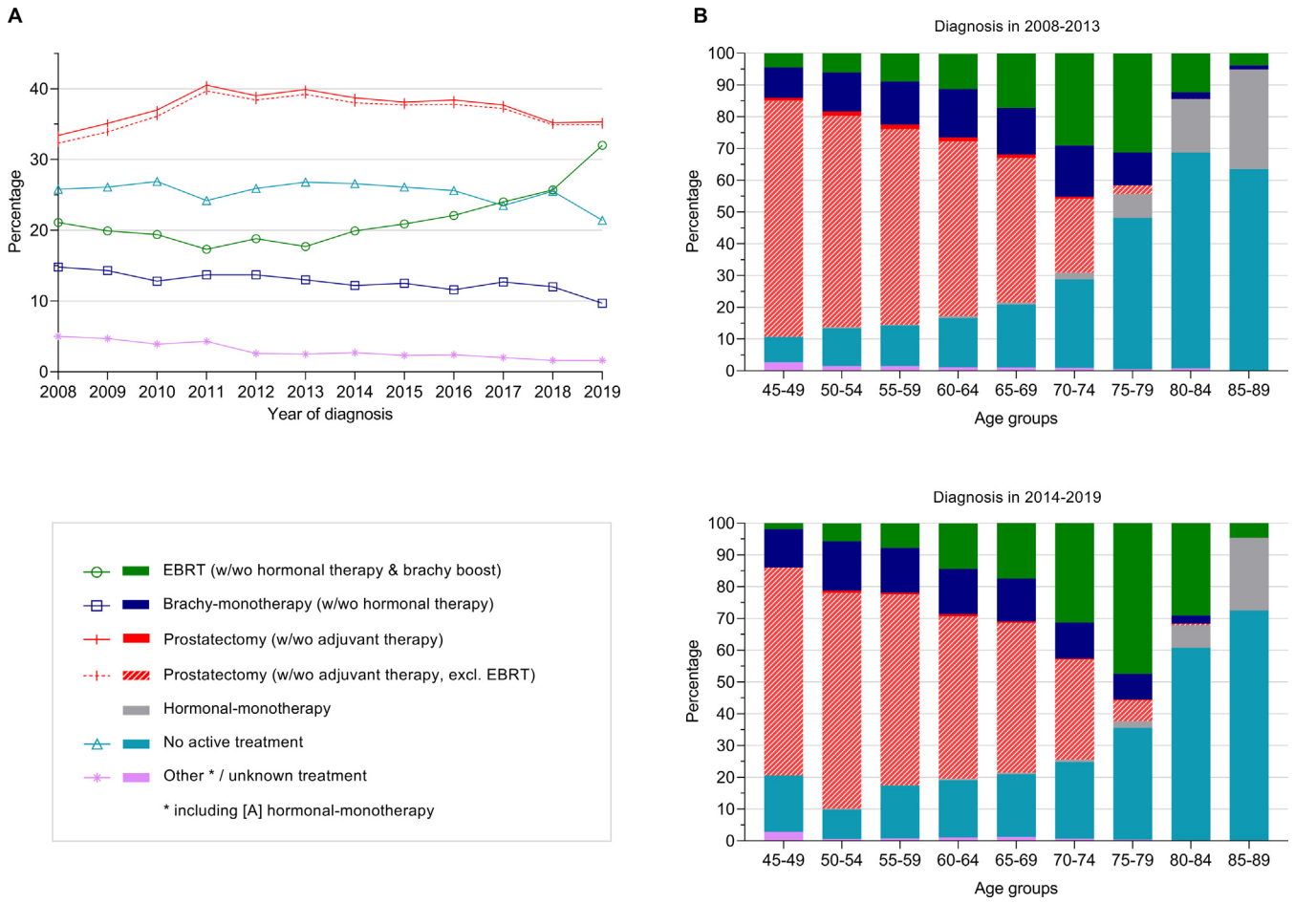

Fig. 2. Primary treatment in patients diagnosed with intermediate-risk localized prostate cancer in The Netherlands [A] over the years of diagnosis, N = 37,767, and [B] according to 5-year age groups stratified for 2008–2013, N = 18,861, and 2014–2019, N = 18,847.

percent of RPs were followed by EBRT. EBRT use mainly increased in men aged 75–84 years. Over time, less patients received hormonal-monotherapy (36 % versus 18 %) and application of no active treatment slightly increased (7–10 %). Hormonal-monotherapy and no active treatment were given mainly in elderly patients.

In multilevel analyses in patients with intermediate or high-risk PCa, use of EBRT versus RP decreased by year of diagnosis in 2008–2013 and increased in 2014–2019 (Table 3). Higher age, more comorbidities and less travel time for EBRT were positively associated with EBRT versus RP in both 2008–2013 and 2014–2019. No significant difference was found between regions, except for the period 2008–2013; the North compared to the South was associated with a higher probability of EBRT. Men with high-risk localized or locally advanced disease were more likely to receive EBRT instead of RP, compared to intermediate-risk disease. A diagnosis in a university hospital or hospital with radiotherapy department was positively associated with EBRT (only in 2014–2019), as was a diagnosis in a hospital where no RP was performed (both in 2008–2013 and 2014–2019). No association was found with volume of hospital diagnoses.

Discussion

This nationwide study investigating primary radiotherapy in PCa treatment in 2008–2019, showed that EBRT use remained stable in low-risk disease and increased in intermediate/high-risk PCa. Brachy-monotherapy use in low/intermediate-risk PCa decreased. Radiotherapy versus no active treatment was associated with cT, age, number of comorbidities, and region. EBRT versus RP was associated with the year of diagnosis, age, number of comorbidities, travel time for EBRT, prognostic risk, type of hospital, and whether the hospital of diagnosis had a radiotherapy department or RP availability.

Low-risk PCa

The decreasing rates of brachy-monotherapy and RP in low-risk PCa coincided with an increasing percentage of patients who underwent no active treatment. Deferred treatment in low-risk disease is nowadays preferred and similar trends towards no active treatment were observed in the USA, Canada, Australia and Sweden [10,18–20].

Patients with higher cT-classification more often received radiotherapy instead of no active treatment. This trend was also observed in Canada [19] and can be explained by the less favorable outcome with increased probability of disease progression [21]. In case of active treatment, older men most often received EBRT while younger ones more often underwent RP or brachy-monotherapy. Our multilevel analyses also showed that EBRT instead of no active treatment is more often received by older compared to younger men, while brachy-monotherapy instead of no active treatment is mainly given to younger ones. As these analyses did not include RP, mainly younger patients receiving active treatment were excluded. Overall, most elderly patients received no active treatment. The observed distribution of treatment modalities across age groups can be explained by EBRT being non-invasive, contrary to brachytherapy and RP. Similar trends across age groups in low-

Fig. 3. Primary treatment in patients diagnosed with [1] high-risk localized prostate cancer in The Netherlands [A] over the years of diagnosis, N = 17,777, and [B] according to 5-year age groups stratified for 2008–2013, N = 9,496, and 2014–2019, N = 8,193, and [2] locally advanced prostate cancer in The Netherlands [A] over the years of diagnosis, N = 24,731, and [B] according to 5-year age groups stratified for 2008–2013, N = 11,198, and 2014–2019, N = 13,408.

risk PCa were observed for other Western countries [10–12,19]. Regional variation in the use of radiotherapy versus no active treatment were found, for which reasons remain unclear. In Canada and Sweden, geographical variation in low-risk PCa treatment were also observed [12,19,20] potentially reflecting disparities in available treatment modalities within the regions [19,20]. In Australia, the use of active surveillance differed between private and public hospitals, possibly related to differences in patient characteristics or hospitals' culture and organization [18]. In our study, however, type of hospital and the treatment modalities available in the diagnosing hospital were not associated with treatment in low-risk PCa in the most recent period.

Intermediate and high-risk PCa

Decreased brachy-monotherapy use in intermediate-risk PCa coincided with increased RP use in 2008–2011, which thereafter decreased, and increased EBRT use in 2014–2019. EBRT and RP also increased in high-risk disease, coinciding decreased non-curative hormonal-monotherapy use. In intermediate and high-risk PCa in the USA and high-risk PCa in Norway, RP use strongly increased as well, although EBRT use remained stable [10,13].

RP is less often considered in advanced disease [22], which is in line with our finding of more frequent EBRT instead of RP in high-risk localized and locally advanced PCa compared to intermediate-risk disease. Nevertheless, current treatment guidelines indicate both EBRT and RP as options in high-risk disease [3–5]. We also found higher age and comorbidities to be associated with a higher likelihood of EBRT versus RP, possibly reflecting treatment decision related to patients' frailty. Similar treatment variation across age groups were seen in Germany and the USA [10,23]. Our analyses further show that the treatment given was associated with the availability of treatment modalities in the diagnosing hospital and with the travel time for EBRT. Also in the UK, the availability of RP and radiotherapy was associated with treatment variation in high-risk PCa; RP was more often applied when available in the diagnosing hospital and patients were more likely to receive brachytherapy following EBRT when brachytherapy was available in the region [24]. Furthermore, in a survey study in the USA, genitourinary oncology physicians' personal level of expertise with brachytherapy was positively associated with the choice for brachytherapy boost [25].

Previous trends and optimal utilization rates

The recent treatment trends in localized PCa differ from trends previously observed in the Netherlands. In 1997–2008, EBRT use decreased, while brachytherapy use increased [9]. Furthermore, decreased use of no active treatment and increased RP use were observed in 1989–2006 [14]. Differences in treatment over time can partly be explained by changed treatment guidelines recommending active surveillance in low-risk PCa [3–6], and may further be caused by the changed availability of radiotherapy and RP. For locally advanced disease, an increasing trend in EBRT was already observed for 1997–2008 [9].

Thompson et al. previously modelled a guideline-based optimal EBRT utilization rate of 51 % in patients with PCa in Western countries [26]. However, for all non-metastatic PCa combined, we observed primary and adjuvant EBRT utilization rates of 28 % and 1 %, respectively. Specifically the modelled rate of EBRT following RP is much higher than the utilization rate observed. The differences may be explained by the modelling study including EBRT in metastatic disease and not addressing the prevalence of prognostic risk groups and treatment protocols in The Netherlands.

Table 3
Adjusted odds ratios (OR) of receiving EBRT versus radical prostatectomy in patients with intermediate and high-risk localized and locally advanced prostate cancer in The Netherlands, stratified for diagnoses in 2008–2013 and 2014–2019.

OR for receiving EBRT versus radical prostatectomy				
	2008–2013 EBRT N = 12,732, Radical prostatectomy N = 10,924		2014–2019 EBRT N = 14,981, Radical prostatectomy N = 12,054	
	OR [A]	(95 %CI)	OR [A]	(95 %CI)
Year of diagnosis (continuously)	**0.95**	**(0.94–0.97)**	**1.03**	**(1.01–1.04)**
Age at time of diagnosis, years				
< 65	Reference		Reference	
65– < 75	**3.39**	**(3.08–3.73)**	**2.61**	**(2.26–3.00)**
≥ 75	**54.03**	**(44.78–65.18)**	**39.33**	**(32.84–47.11)**
Number of comorbidities at diagnosis [B]				
0	Reference		Reference	
1	**1.41**	**(1.18–1.68)**	**1.43**	**(1.18–1.73)**
≥ 2	**2.17**	**(1.80–2.63)**	**2.24**	**(1.84–2.71)**
Geographical region				
North	Reference		Reference	
East	0.79	(0.58–1.06)	0.91	(0.69–1.19)
South	**0.68**	**(0.48–0.95)**	0.88	(0.65–1.19)
South West	0.77	(0.55–1.07)	0.83	(0.62–1.12)
North West	0.76	(0.57–1.02)	0.85	(0.65–1.11)
Travel time (car) for EBRT, minutes				
< 15	Reference		Reference	
15–30	0.90	(0.81–1.00)	**0.91**	**(0.85–0.96)**
> 30	**0.85**	**(0.73–0.99)**	**0.88**	**(0.78–0.99)**
Prognostic risk groups				
Intermediate-risk localized	Reference		Reference	
High-risk localized	**2.22**	**(1.92–2.56)**	**1.51**	**(1.33–1.71)**
Locally advanced high-risk	**14.23**	**(12.20–16.59)**	**5.61**	**(4.97–6.33)**
Type of hospital				
University [C]	Reference		Reference	
Non-university	0.98	(0.65–1.48)	**0.69**	**(0.49–0.97)**
Radiotherapy department embedded in the hospital				
No	Reference		Reference	
Yes	1.22	(0.80–1.87)	**1.42**	**(1.09–1.86)**
Prostatectomies are performed in the hospital				
No	Reference		Reference	
Yes	**0.82**	**(0.67–0.99)**	**0.61**	**(0.50–0.73)**
Volume of intermediate/high-risk localized and locally advanced PCa diagnoses in the hospital [D]				
Low volume	Reference		Reference	
High volume	1.05	(0.80–1.36)	1.13	(0.94–1.35)

OR: odds ratio, EBRT: external beam radiotherapy, 95 %CI: 95 % confidence interval, PCa: prostate cancer; values in bold are statistically significant

[A] Models with both a random intercept and random effect were applied for the analyses on age, number of comorbidities (2014–2019), region (2014–2019), travel time for EBRT (2008–2013), prognostic risk groups and prostatectomies performed in the hospital. The analyses on year of diagnosis, and travel time for EBRT (2014–2019) were not adjusted, as none of the variables fulfilled the criteria for inclusion in the adjustment set. The analyses on number of comorbidities, travel time for EBRT (2008–2013), and prognostic risk group was adjusted for age. The analyses on age, region (2014–2019), volume of diagnoses in the hospital (2008–2013), and prostatectomies performed in the hospital (2014–2019) were adjusted for prognostic risk group. The analysis on region (2008–2013) was adjusted for age and prognostic risk group. The analysis on type of hospital (2008–2013) was adjusted for age and travel time for EBRT. The analyses on type of hospital (2014–2019), and radiotherapy department in the hospital (2014–2019) were adjusted for age and prostatectomies performed in the hospital. The analysis on radiotherapy department in the hospital (2008–2013) was adjusted for age, travel time for EBRT and type of hospital. The analysis on volume of diagnoses in the hospital (2014–2019) was adjusted for prostatectomies performed in the hospital. The analysis on prostatectomies performed in the hospital (2008–2013) was adjusted for year of diagnosis and prognostic risk group. Comorbidities were not included in adjustment sets considering their limited availability. The analysis on type of hospital was not adjusted for a radiotherapy department in the hospital, as this was considered a basic component of university hospitals.

[B] Comorbidities were available for patients diagnosed in the South before 2015 and for all patients diagnosed in October 2015-March 2016.

[C] Including the single cancer specific hospital in The Netherlands.

[D] Patients diagnosed in the 50 % of hospitals with the lowest annual average number of intermediate/high-risk localized and locally advanced prostate cancer diagnoses: <75 patients in 2008–2013 and < 78 patients in 2014–2019, were categorized in low volume. The remaining patients in the high volume-category.

For RP and brachytherapy, observed (27 % and 8 %, respectively) and modelled optimal rates (24 % and 9 %, respectively) were comparable [26], as was our observed primary EBRT rate with observations from Norway in 2006–2015 (26 %) and the USA in 2004–2014 (27 %-29 %) [10,13]. Future research should further explore the similarities and disparities of radiotherapy use in prostate cancer treatment across Western/European countries.

Strengths and limitations

Strengths of our study include using nationwide population-based data and providing a unique overview of radiotherapy use in non-metastatic PCa in The Netherlands for 12 recent years. Limitations include not being able to distinguish active surveillance from watchful waiting. Nevertheless, patients receiving no active treatment, having low or intermediate-risk PCa and no limited life expectancy, most likely were managed with active surveillance, while watchful waiting was more likely in the other patients. Also no distinction could be made between conventional and robot-assisted RP, as surgical techniques performed were limitedly registered in our study period. Furthermore, the analyses could not be adjusted for comorbidities given their limited availability. This may have resulted in residual confounding, especially in associations found for age. In patients who underwent RP before 2013,

the pretreatment assessment of prognostic risk may be over- or (to a lesser extent) underestimated [27] in our study, because only resection specimen-based GS were available at that time. Changed diagnostic procedures, including targeted biopsies, MRI and PSMA-PET scans [28], furthermore improved staging in the study period. Consequently, stage shifts occurred which probably changed the overall distribution of treatments applied. For the reported treatment trends stratified for risk groups, however, no major changes due to improved diagnostic procedures are expected. Finally, variation in prognostic risk group classification exists within The Netherlands, causing differences in risk group assessment between our study and some Dutch hospitals.

Conclusions

Over time, an increasing percentage of patients with intermediate and high-risk PCa received curative-intent treatment. EBRT gained a more prominent place in treatment of intermediate/high-risk PCa, while use of brachy-monotherapy in intermediate-risk PCa diminished. RP was increasingly applied in high-risk PCa. Specific groups of patients and those diagnosed in hospitals with a radiotherapy department or where no RPs were performed, more likely received EBRT instead of RP. This variation suggests both treatment decision related to patients and disease characteristics and to the availability of treatment modalities in the hospitals of diagnosis. In low-risk PCa, more patients refrained from active treatment. EBRT use remained limited and the use of brachy-monotherapy and RP decreased. Variation in use of radiotherapy instead of no active treatment suggests that the choice for active treatment with EBRT/brachy-monotherapy is related to patient and tumor characteristics. No variation was observed for hospital characteristics in the most recent period, suggesting adherence to the recommendation of deferred treatment irrespective of the treatment modalities available.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors thank the registration team of the Netherlands Comprehensive Cancer Organisation (IKNL) for the collection of the data for the Netherlands Cancer Registry, J.S.F. Maurits for the advice on multilevel analyses, and J.L. Evans for proofreading the manuscript.

This work was funded by the Dutch Association of Radiation Oncology (NVRO) which had the opportunity, thanks to external funding, to financially support our study.

References

[1] Sung H et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209–49.
[2] Netherlands Comprehensive Cancer Organisation (IKNL). *Prostate cancer in the Netherlands: an overview based on the Netherlands Cancer Registry (1989 - 2020)*. [cited 2022 January, 17th]; Available from: https://iknl.nl/prostaatkanker-in-nederland.
[3] European Association of Urology, *Guidelines on prostate cancer*. 2021.
[4] Nederlandse Vereniging voor Urologie, *Richtlijn prostaatcarcinoom*. 2014.
[5] National Comprehensive Cancer Network, *NCCN Clinical practice guidelines in oncology: prostate cancer*. 2022.
[6] Morash C et al. Active surveillance for the management of localized prostate cancer: guideline recommendations. Can Urol Assoc J 2015;9:171–8.
[7] Preisser F et al. Intermediate-risk prostate cancer: stratification and management. Eur Urol Oncol 2020;3:270–80.
[8] Moris L et al. Benefits and risks of primary treatments for high-risk localized and locally advanced prostate cancer: an international multidisciplinary systematic review. Eur Urol 2020;77:614–27.
[9] Poortmans PM et al. A population-based study on the utilisation rate of primary radiotherapy for prostate cancer in 4 regions in the Netherlands, 1997–2008. Radiother Oncol 2011;99:207–13.
[10] Burt LM, Shrieve DC, Tward JD. Factors influencing prostate cancer patterns of care: an analysis of treatment variation using the SEER database. Adv Radiat Oncol 2018;3:170–80.
[11] Morias S et al. Variation in radiotherapy patterns of care in the radical treatment of South Australian men with non-metastatic prostate cancer between 2005–2015. Radiother Oncol 2020;145:138–45.
[12] Sandoval C et al. Treatment patterns among Canadian men diagnosed with localized low-risk prostate cancer. Curr Oncol 2015;22:427–9.
[13] Fossa SD et al. Definitive radiotherapy for prostate cancer in Norway 2006–2015: Temporal trends, performance and survival. Radiother Oncol 2021;155:33–41.
[14] Cremers RG et al. Prostate cancer: trends in incidence, survival and mortality in the Netherlands, 1989–2006. Eur J Cancer 2010;46:2077–87.
[15] Signaleringscommissie Kanker van KWF Kankerbestrijding, *Kwaliteit van kankerzorg in Nederland: voortgang en blik op de toekomst*. 2014.
[16] ProZIB stuurgroep, *ProZIB eindrapportage: prostaatkankerzorg in Nederland*. 2019.
[17] GEODAN. *Afstanden tussen postcodes*. 2021 [cited 2022 April, 6th]; Available from: https://ontwikkel.geodanflolegal.nl/blog/wat-is-reistijdentabel-drive-time-matrix/.
[18] Weerakoon M et al. The current use of active surveillance in an Australian cohort of men: a pattern of care analysis from the Victorian prostate cancer registry. BJU Int 2015;115:50–6.
[19] Roy S et al. Active treatment in low-risk prostate cancer: a population-based study. Curr Oncol 2019;26:e535–40.
[20] Beckmann K et al. Radical radiotherapy for prostate cancer: patterns of care in Sweden 1998–2016. Acta Oncol 2020;59:549–57.
[21] Herden J, Wille S, Weissbach L. Active surveillance in localized prostate cancer: comparison of incidental tumours (T1a/b) and tumours diagnosed by core needle biopsy (T1c/T2a): results from the HAROW study. BJU Int 2016;118:258–63.
[22] Veeratterapillay R et al. Radical prostatectomy for locally advanced and metastatic prostate cancer. Ann R Coll Surg Engl 2017;99:259–64.
[23] Hager B et al. Increasing use of radical prostatectomy for locally advanced prostate cancer in the USA and Germany: a comparative population-based study. Prostate Cancer Prostatic Dis 2017;20:61–6.
[24] Parry MG et al. Impact of cancer service centralisation on the radical treatment of men with high-risk and locally advanced prostate cancer: a national cross-sectional analysis in England. Int J Cancer 2019;145:40–8.
[25] McClelland 3rd S et al. Dramatically polarized opinion on the role of brachytherapy boost in management of high-risk prostate cancer: a survey of North American genitourinary expert radiation oncologists. Clin Genitourin Cancer 2018;16:e543–5.
[26] Thompson SR et al. Estimation of the optimal utilisation rates of radical prostatectomy, external beam radiotherapy and brachytherapy in the treatment of prostate cancer by a review of clinical practice guidelines. Radiother Oncol 2016;118:118–21.
[27] Cohen MS et al. Comparing the gleason prostate biopsy and gleason prostatectomy grading system: the lahey clinic medical center experience and an international meta-analysis. Eur Urol 2008;54:371–81.
[28] Descotes JL. Diagnosis of prostate cancer. Asian J Urol 2019;6:129–36.